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PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

RUFFLES, Graham Keith
MARKS & CLERK
66-68 Hills Road
Cambridge CB2 1LA
GRANDE BRETAGNE

ENTERED ONTO INPROMA
Date: 18/10/4 Initials: LG

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.10.2004
Applicant's or agent's file reference WPP286385	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/03327	30.07.2003	30.07.2002

Applicant
PHARMA MAR, S.A.U. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hebert, W Tel. +49 89 2399-2152

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WPP286385	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03327	International filing date *(day/month/year)* 30.07.2003	Priority date *(day/month/year)* 30.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D407/06		
Applicant PHARMA MAR, S.A.U. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.02.2004	15.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Goss, I Telephone No. +49 89 2399-8292

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/03327

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-112 as originally filed

Claims, Numbers

1-49 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24

because:

☒ the said international application, or the said claims Nos. 24 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-49
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2-22,24-37,39-49
	No:	Claims	1,23,38
Industrial applicability (IA)	Yes:	Claims	1-23,25-49
	No:	Claims	24

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 24 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty

The present application relates to myriaporones analogues and their use as medicaments for the treatment of cancer. Myriaporones are natural polyketide-derived products isolated from the bryozoan Myriapora truncata. The present application represents an attempt at the total synthesis of myriaporones and derivatives according to general formula (I) with the proviso that the natural compounds described in D1:US-A-5 514 708 (RINEHART KENNETH L ET AL) 7 May 1996 are excluded.
The synthetic route involves i.a. removing a protecting group from a compound of formula **5a** wherein at least one group R is a protecting group to give the corresponding compound of formula **5b** where the said at least one group R is hydrogen and preferable at least one of the R substituents is not hydrogen.
According to schemes 1 as well as 2 the same method of producing compounds of formula I is shown whereby according to scheme 2, a different stereochemistry in the oxazolidinone 9 (which is R in scheme 1 and S in scheme 2) or oxazolidinone 21.

None document of the cited prior art describes a total synthetic route for the production of myriaporones. Novelty can be thus acknowledged.

Inventive step

The problem underlying the present application appears to reside in the provision of myriaporone analogues via an efficient, stereo controlled total synthetic route for their production.
D1 only describes fractionation and purification of active components from the methanol extract of the bryozoan Myriapora truncata. Among those metabolites

isolated, compounds MT-332 (compounds 3 and 4) and compound MT-381 and MT-381-B (compounds 1 and 2 respectively) are the ones which exhibit pronounced cytotoxicity.
D2:TAYLOR R E ET AL: "A Divergent Approach to the Myriaporones and Tedanolide: Enantioselective Preparation of the Common Intermediate" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 51, 17 December 1998 (1998-12-17), pages 9361-9364, XP004144201, which has been referred to by the applicant in the description page 1, relates to the asymmetric preparation of a potential intermediate in the total synthesis of myriaporones. However a lack of stereoselectivity has been observed.
According to the other documents cited only C(x)-C(y) segments of the whole natural product(s) were synthesised which each represented a progress toward the total synthesis of myriaporones.
The problem has been solved by the synthetic route providing compounds of general formula (I).
Data are given in terms of yields, achievement of the desired stereochemistry as well as inhibition of cell growth the latter obtained from different human cancer types.

However, a favourable IPER cannot be issued and Applicant's attention is drawn to the following remarks:
a) terms such as "alkyl, alkynyl, aryl or heteroaryl being optionally further substituted" used i.a. in claim 1, are considered to be non-limitative and embrace an infinite number of possibilities not yet ex- plored by the Applicant; they should therefore be limited to the specific meanings given in the description as otherwise it will be difficult to ascertain if the problem has been indeed solved by all the compounds claimed considered as obvious modifications or equivalents to one or more particular examples.
b) The reference to D1 at the end of claim 1 should be avoided and replaced by the compounds names (eg ".. that the compound is not the natural compound designated as MT332 or MT 381...").
c) "Prodrug"- Protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. There is no specific indication within the application as to what may be a prodrug, nor is a prodrug a definable term as regards the structure of such a compound. The skilled person has no indication as to what falls within this definition.

Industrial applicability
The patentability can also be dependent upon the formulation of the claims. The EPO,

for example, does not recognize as industrially applicable the subject- matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.